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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/588,028	04/30/2007	Himanshu Brahmbhatt	060348-0149	1320

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EXAMINER	
SINGH, ANOOP KUMAR	

ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/588,028	BRAHMBHATT ET AL.	
	Examiner	Art Unit	
	ANOOP SINGH	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 December 2011*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *8,10-15,17,18,20-22 and 31-36* is/are pending in the application.

5a) Of the above claim(s) *31-36* is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *8,10-15,17,18 and 20-22* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

12)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/30/2011, 8/18/2010 and 2/18/2010* .
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/14/2010 has been entered.

Applicant's arguments filed August 8 and declaration filed on December 14, 2010 have been received and entered. Claim 8 has been amended, while claims 1-7, 9, 16, 19, 23-29 and 30 have been canceled. It is noted that applicant has newly added withdrawn composition claims. The status identifier of claims 31-36 is incorrect and should be identified as new claims as claims 31-36 were never entered. Newly submitted claims 31-36 are directed to claims similar to previously submitted claims 1-7 composition claims that were withdrawn without traverse in office action mailed on March 18, 2009.Since applicant has received an action on the merits for the originally presented invention, and this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 31-36 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Currently, claims 8, 10-15, 17-18, 20-21 and 22 are under consideration.

Election/Restrictions

Applicants' election without traverse of claims 8-33 and 38 (Group II) in the reply filed on January 15, 2009 was acknowledged. Claims 8, 10-15, 17-18, 20-21 and 22 drawn to a targeted drug delivery method are under examination.

Information Disclosure Statement

The information disclosure statements (IDS) submitted on 6/30/2011, 8/18/2010 and 2/18/2010 are in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statements have been considered by the examiner.

Oath/Declaration

The Brahmbhatt's declaration filed on December 14, 2010 under 37 CFR 1.132 is not fully sufficient to overcome the rejection of claims 8, 10-12, 15, 17-19, 21 and 22 based upon the reference of Sabbadini et al. (US 7,183,105, dated 2/27/2007, filed 5/28/2002, effective filing date 2/25/2002) Khatchatourians et al (Preparative Biochemistry, 3(3) 1973, 291-298) and Christen et al (Gene, 1983, 23, 195-198) and Nikaido et al, applied under 35 U.S.C. 103(a). The declaration will be discussed in detail below as it applies to the new rejection.

Withdrawn-Claim Rejections - 35 USC § 102

Claims 8, 10-12, 15, 17-19, 21 and 22 were rejected under 35 U.S.C. 102(e) as being anticipated by Sabbadini et al. (US 7,183,105, dated 2/27/2007, filed 5/28/2002, effective filing date 2/25/2002). Applicants' cancellation of claim 19 renders its rejections moot. In view of Applicants' amendment of base claim 8, introducing the limitation "minicell that are approximately 400nm in diameter", that is not explicitly taught by Sabbadini et al., the previous rejection is rendered moot and hereby withdrawn.

Withdrawn-Claim Rejections - 35 USC § 103

Claims 8, 11, 13-14 were rejected under 35 U.S.C. 103(a) as being unpatentable over Sabbadini et al. (US 7,183,105, dated 2/27/2007, filed 5/28/2002, effective filing date 2/25/2002), Nettelbeck et al (Mol Ther. 2001; 3(6):882-91, IDS) and Coldwell et al (The Journal of Immunology, 1984, 133, 2 950-957). In view of Applicants' amendment of base claim 8, introducing the limitation "minicell that are approximately 400nm in diameter", that is not explicitly taught by Sabbadini et al., the previous rejection is rendered moot and hereby withdrawn.

Claims 8, 20 were rejected under 35 U.S.C. 103(a) as being unpatentable over Sabbadini et al. (US 7,183,105, dated 2/27/2007, filed 5/28/2002, effective filing date 2/25/2002) and Hope

et al (WO/1996/026715, dated 06/09/1996, IDS). In view of Applicants' amendment of base claim 8, introducing the limitation "minicell that are approximately 400nm in diameter", that is not explicitly taught by Sabbadini et al., the previous rejection is rendered moot and hereby withdrawn.

New-Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 8, 10-12, 15, 17-18, 20-21 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sabbadini et al. (US 7,183,105, dated 2/27/2007, filed 5/28/2002, effective filing date 2/25/2002), Khatchatourians et al (Preparative Biochemistry, 3(3) 1973, 291-298) and Christen et al (Gene, 1983, 23, 195-198) and Nikaido et al (Microbiol. Mol. Biol. Rev.2003, 67, 593–656).

The bispecific ligand comprising first arm that carries specificity for minicells surface and a second arm that carries specificity for cell surface receptor has been interpreted as being equivalent to the attachment of an antibody that binds to a ligand specific to a minicell as well as receptor on to the mammalian cell surface, as first and second arm respectively.

With respect to claims 8, 10-12, Sabbadini et al. teach a targeted drug delivery method comprising contacting a target non-phagocytic mammalian cell with an intact bacterially derived minicell coated with an antibody as a binding moiety capable of binding to a ligand present on the surface of the target mammalian cell, wherein the minicell comprises the small molecule, and wherein the contents of the minicell are delivered into the cell from a minicell bound to the cell (col. 17, 6-15, col. 7, lines 10-15, col. 136, lines 58-66 , table 9 and claim 1). It is noted that Sabbadini et al disclose mammalian cell surface display receptor such as EGFR that is capable of activating receptor mediated endocytosis with minicell (see example 19). Sabbadini et al also teach contacting target non-phagocytic tumor cells with intact minicells containing toxic drug

molecule coated with an antibody that is capable of binding a ligand on the surface of the tumor cell, wherein minicells are engulfed by the tumor cell by receptor mediated endocytosis, thereby releasing toxic drug into the tumor cell (see column 171, col. 1, line 62-65). Sabbadini et al. also teach that the minicells of the invention are capable of encapsulating and/or loading into a membrane a variety of substances that includes small molecules (see column 161, lines 37-46, column 17, line 16). It is further disclosed that for therapeutic purposes minicells can display or encapsulate small molecules in the treatment of variety of disorder (see col. 37). Sabbadini et al teach that the minicells are engulfed by cells by a process such as receptor mediated endocytosis (see col. 171, line 55). Additionally, it is also disclosed that the method results in transfer of the molecule from the interior of a minicell into the cytoplasm of the target cell (see col. 24, line 22, col. 165, lines 5-10). Drug loading of minicells is likely by diffusion down a concentration gradient with entry via nonspecific porin channels in the outer membrane as taught by Nikaido et al. Sabbadini et al disclose that the target mammalian cell may include A-431 cancer cell lines that are non-phagocytic mammalian cell (column 252, line 30 and 55). It is also disclosed that the cell displays a ligand specifically recognized by a binding moiety attached to the minicell. The moiety to be conjugated to the minicells can be a polypeptide (limitation of claim10). It is also disclosed that an antibody can be covalently attached as a binding moiety (see column 136, lines 58-66), which binds to ligand present on the surface of a mammalian cell. Thus, bispecific ligand comprises a covalent attachment of an antibody that binds to a ligand specific of a minicell outer membrane protein as well as receptor on to the mammalian cell surface, as first and second arm respectively (limitation of claims 11 and 15). Sabbadini et al also teach minicell comprising a therapeutic agent displays a binding moiety such as antibody that specifically binds a receptor present on the surface of a non-phagocytic cell meeting the limitation of first and second arm being monospecific (col. 7, lines 6-15, limitation of claim 12). Sabbadini et al teach that the antibody may be a single chain antibody (see col. 132, line 60) or a humanized antibody (col. 132, line 53) (limitation of claims 17 -18). With respect to claims 21-22, Sabbadini et al. teach that method of targeted drug delivery using minicell can be carried out under *in vitro* or *in vivo* condition (see col. column 11, line 14 and col. 36, lines 56-59). Sabbadini et al. teach a method of small molecule delivery by providing a composition of minicells and covalently attaching binding moieties including antibody to said minicells via membrane proteins that binds

to a ligand present on the surface of a mammalian cell, but differed form claimed invention by not explicitly disclosing that minicell are 400nm in diameter.

Khachatourians teaches a preparation of purified bacterial minicells by causing the separation of minicells from normal, contaminating bacterial cells by inducing the normal cells to filamentate followed by selective elimination of the filamentous bacteria (page 297). Khachatourians teaches obtaining high yield of minicell by sucrose gradient centrifugation, but differ from claimed invention by not filtering the contaminants by using 0.45 micron to obtain a purified population of approximately 400nm minicell.

However, prior to instant invention, purification of minicell by Millipore filtration system was known in prior art. Christen et al disclose the low yield of purified minicell of 400nm could be produced by employing 0.45 micron meter filter (see page 197, col. 1, para. 3).

Therefore, it would have been *prima facie* obvious for a person of ordinary skill in the art to combine the respective teachings of Sabbadini et al, Nikaido , Khachatourians et al and Christen to optimize the purity of the minicell composition of Sabbadini using the well-known means in the art for minicell purification to remove any other potentially harmful contaminants using method disclosed by Khachatourians et al and Christen, in a method of targeted small molecule delivery with a reasonable expectation of success, at the time of the instant invention. A person of skill in the art would have been motivated to employ filtration followed by gradient centrifugation in order to remove other potentially harmful contaminants as a matter of design choice to obtain more specific delivery of therapeutic agent as described by Khachatourians et al and Christen, said design choice amounting to combining prior art elements according to known methods to yield predictable results. One who would have practiced the invention would have had reasonable expectation of success since Sabbadini et al had already taught a method for delivery of small molecule by attaching an antibody to a bacterial minicells that specifically binds a ligand present on the surface of a mammalian cell, while combining the teaching of Sabbadini et al with those of Khachatourians et al, Christen and Nikaido would have resulted in encapsulation of therapeutic effective concentration of small molecule drug in minicell of approximately 400 nm minicell via a concentration gradient with entry via nonspecific porin channels in the outer membrane as taught by Nikaido. In the instant case, the prior art as a whole teaches that one should use any means known and necessary to eliminate the vegetative cells

from the minicells in a desired minicell prep- typically and ultimately using the size differential of the minicell and the undesired contaminants to purify the minicells. As such the claimed invention was obvious at the time the invention was made.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Claims 8, 11-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sabbadini et al. (US 7,183,105, dated 2/27/2007, filed 5/28/2002, effective filing date 2/25/2002), Khatchatourians et al (Preparative Biochemistry, 3(3) 1973, 291-298), Christen et al (Gene, 1983, 23, 195-198), Nikaido et al (Microbiol. Mol. Biol. Rev.2003, 67, 593–656), Nettelbeck et al (Mol Ther. 2001; 3(6):882-91, IDS) and Coldwell et al (The Journal of Immunology, 1984, 133, 2 950-957).

The teaching of Sabbadini, Khatchatourians, Christen and Nikaido have been described above and relied in same manner here. The combination of references teach a method of drug delivery by covalently attaching binding moieties such as antibody to minicells of approximately 400nm such that it binds to a ligand present on the surface of a mammalian cell, but differ from claimed invention by not explicitly disclosing that the first arm specific to an O-polysaccharide component of LPS or first and second arm are multivalent.

However, prior to instant invention, Nettelbeck et al teach a recombinant antibody as a molecular bridge, linking the virus capsid to the endothelial cell surface protein endoglin, for vascular targeting of adenoviruses (abstract). It is noted that Nettelbeck et al also disclose a method to construct bispecific single chain multivalent antibody directed against endoglin and the adenovirus knob domain (see 885, col.1, para.4). It is also disclosed that the ScFv C4 (endoglin) and the neutralizing anti-knob scFv S11 are combined in a bispecific single-chain diabody (scDb EDG-Ad) (see figure 3) for experimental analysis. Nettelbeck et al reported enhanced oviral infectivity mediated by scDb EDG-Ad that was restricted to endoglin-positive cells showing cell specific targeting (see figure 6, page 889, col. 2, para. 2).

Although Nettelbeck et al describes the advantage of using bispecific diabody to target viral fiber knob domain to endoglin expressing cancer cell, but differed from claimed invention by not disclosing first arm specific to an O-polysaccharide of a LPS.

Prior to instant invention, Coldwell et al teach production of monoclonal antibodies to antigenic determinants of the O-polysaccharide of *Salmonella typhimurium* lipopolysaccharide (LPS) (abstract).

Therefore, it would have been *prima facie* obvious for a person of ordinary skill in the art to combine the respective teachings of Sabbadini, Khatchatourians ,Christen, Hope, Nettelbeck et al and Coldwell by using an antibody to bring together intact minicell and mammalian cell such that minicell binds to mammalian cell and minicell that are engulfed by the mammalian cell with a reasonable expectation of success, at the time of the instant invention. A person of skill in the art would have been motivated to use an single chain antibody diabody as a molecular bridge, linking the O-polysaccharide of the minicell to the endothelial cell surface protein endoglin (diabody) as a matter of design choice to obtain more specific delivery of therapeutic agent as described by Nettelbeck, said design choice amounting to combining prior art elements according to known methods to yield predictable results. One who would have practiced the invention would have had reasonable expectation of success since Sabbadini et al had already taught a method for targeted delivery of small molecule by attaching an antibody to a bacterial minicells that specifically binds a ligand present on the surface of a mammalian cell, while combining the teaching of Sabbadini et al with those in Nettelbeck and Coldwell would have resulted in specific small molecule transfer into endoglin positive endothelial cell.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Claims 8, 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sabbadini et al. (US 7,183,105, dated 2/27/2007, filed 5/28/2002, effective filing date 2/25/2002), Nikaido et al (Microbiol. Mol. Biol. Rev.2003, 67, 593–656), Khatchatourians et al (Preparative Biochemistry, 3(3) 1973, 291-298), Christen et al (Gene, 1983, 23, 195-198) and Hope et al (WO/1996/026715, dated 06/09/1996, IDS)

The teaching of Sabbadini, Nikaido, Khatchatourians and Christen have been described above and relied in same manner here. The combination of references teach a method of drug delivery by covalently attaching an antibody to minicells capable of encapsulating into a membrane via simple diffusion a small molecules, wherein said antibody at the surface of minicell binds to a ligand present on the surface of a mammalian cell, but differ from claimed invention by not teaching encapsulation of a chemotherapeutic agent.

However, prior to instant invention, it was routine in the art to package/load chemotherapeutic drugs such that diffusion across the phospholipid bilayer-membrane is unidirectional for targeted delivery of the molecule. For instance, Hope et al teach a method a method involves loading a chemotherapeutic agent such as doxorubicin into preformed lipid bilayer of liposome having a concentration gradient across the lipid bilayer (see Figure 1). It is noted that Hope et al disclose that the structure of the lipid bilayer is similar to the membranes enveloping animal cells (see page 1, line 21).

Therefore, it would have been *prima facie* obvious for a person of ordinary skill in the art to combine the respective teachings of Sabbadini et al, Nikaido, Khatchatourians, Christen and Hope by modifying the method of targeted drug delivery of Sabbadini et al by loading chemotherapeutic agent such as doxorubicin into minicell using as disclosed by Hope by simple diffusion as per the teaching of Nikaido, with a reasonable expectation of achieving predictable result. A person of skill in the art would have been motivated to encapsulate doxorubicin into the minicell because Sabbadini et al embraced the potential of delivering cytotoxic agent specifically to the tumor for cancer therapy (supra). One who would have practiced the invention would have had reasonable expectation of success since Nikaido had already taught a loading of drugs in bacterial cells primarily occurs via simple diffusion, while Sabbadini et al disclosed that cellular membrane of the minicell is a lipid bilayer that forms the boundary between the interior of a cell and its external environment. Thus, it would have required routine experimentation for one of ordinary skill in the art to combine the teachings of Sabbadini et al with those of Nikaido and Hope to load doxorubicin or any other acidic or basic chemo therapeutic in the bacterial minicell for targeted drug delivery to enhance the therapeutic effect.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Response to arguments

To the extent that Applicants' arguments are pertinent to the new rejections, they are addressed as follows:

Applicant arguments and declaration filed August 18, 2010 and December 14, 2010 have been fully considered but are found not fully persuasive.

Applicant argues that Sabbadini does not disclose a minicell loaded with a therapeutically significant concentration of a small drug. Thus, Sabbadini must fail as 102 reference (see pages 6- 7 of the arguments).

As an initial matter it is noted that Applicants' amendment of base claim 1, introducing the limitation "minicell that are approximately 400nm in diameter", that is not explicitly taught by Sabbadini et al., the previous rejection of anticipation is rendered moot. Applicants' arguments with respect to the withdrawn anticipation rejections are thereby rendered moot.

To the extent argument pertains to the pending new rejection, Applicants' arguments have been fully considered but are not fully persuasive because Sabbadini et al. specifically teaches the method of bringing a target non-phagocytic mammalian cell with a minicell coated with an antibody as a binding moiety capable of binding to a ligand present on the surface of the target mammalian cell, wherein the bacterially derived intact minicell comprises the small molecule, and wherein the contents of the minicell are delivered into the cell from a minicell bound to the cell (col. 17, 6-15, col. 7, lines 10-15, col. 136, lines 58-66). Contrary to applicants' assertion, Sabbadini et al. clearly teaches in vivo therapeutic uses of minicells that may either contain (encapsulate) small molecule, nucleic acid, radionuclides or image-enhancing molecule all of which could be used for therapeutic an vivo or for in vitro assays (see col. 37). To the extent, Sabbadini et al. disclose loading small therapeutic molecule in the minicell, it is applicable to the instant rejection. Applicants' selective reading of Sabbadini et al ignores the teachings of the Nikaido reference. There is no requirement for Sabbadini et al. to teach that which is clearly taught by Nikaido et al. A person of skill in the art would be recognize that small molecule could be loaded in bacterial minicell via simple diffusion as per the teaching of Nikaido and optimize the effective concentration of therapeutic agent of small molecule by

selecting the appropriate loading dosage of a drug depending upon type of drug under consideration, with a reasonable expectation of success.

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., membrane bleb that are less than 0.2 um, page 7 of the arguments) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

On pages 8-10 and 11, paragraph 1-4, applicant argues that Hope et al summary, there is a substantial, art-recognized differences separating liposomes from intact, bacterially-derived minicells, as recited. Further, the Hope method clearly is inapplicable to such minicells. Given these considerations, an asserted similarity between liposomes and cells in relation to membrane structure, vis-a-vis the orientation of constituent lipids, would not have suggested that the Hope methodology somehow might work for intact, bacterially-derived miniceIls. Applicant further argues that it was "surprising that minicells are unable to expel drugs from their cytoplasm, because live bacterial cells extrude noxious chemicals that enter into the bacterial cytoplasm. Applicant further assert that another unexpected aspect of the present invention is that *therapeutically significant drug concentrations* can be packaged within minicells, because bacterial cytoplasm (and, hence, minieellcytoplasm) contains significant concentrations of biocompatible solutes. Applicant further argues that it was unexpected that drug-packaged minieellS do not leak drug into extracellular space *(id.* at page 10, line 29-30) and the drug-packaged minicell can avoid degradation. *Id.* at page 11, lines 17 and 18.

Such is found persuasive in part as examiner would agree in part that method of loading drugs in a bilayer membrane as disclosed by Hope is not the same as one disclosed in the instant application, however, newly applied art summarized by the reference of Nikaido et al clearly teaches that drug loading in bacterial cell is likely by diffusion down a concentration gradient with entry via nonspecific porin channels in the outer membrane (supra). Therefore, disclosure of minicell of Sabbadini comprising small therapeutic molecule is enabling for the encapsulating small molecule in minicells in view of teaching of Nikaido et al. With respect to applicants' argument that it was "surprising that minicells are unable to expel drugs from their cytoplasm", it

should be noted that prior art generally recognized that porins have revealed charged residues within the channels resulting in a transversal electric field that separates polar and nonpolar solutes (See Nikaido et al). It is generally known that polar solutes are thought to be oriented in the field during permeation, which therefore becomes a fast one dimensional diffusion process (Schulz, 1993, Curr. Opin. Cell Biol. 5, 701–707). Thus, diffusion of polar solute is expected to be a fast one dimensional diffusion process. Therefore the fact that polar solute are thought to be oriented in the field during permeation, which therefore becomes a fast one dimensional diffusion process is an expected result, and is the goal behind encapsulating an agent in the bacterial cell without any leakage or efflux. As indicated in MPEP 716.02(c), Where the unexpected properties of a claimed invention are not shown to have a significance equal to or greater than the expected properties, the evidence of unexpected properties may not be sufficient to rebut the evidence of obviousness. *In re Nolan*, 553 F.2d 1261, 1267, 193 USPQ 641, 645 (CCPA 1977). "

On pages 11 and 12 of the applicants; argument, applicant assert that it is not surprising, therefore, that the inventors' findings were published as a well-received article in the prestigious journal, *Cancer Cell.* See MacDiarmid *et al., Cancer Cell* I1 : 431-45 (2007). The surprising character of the published results, as with the presently claimed invention, prompted an editorial in *Nature Reviews Drug Discovery,* which features that invention. Flemming, *Nature Reviews Drug Discovery* 6:519 (2007), thus concluded that "these results might form the basis of a robust and versatile drug carrier system." Likewise highlighting the claimed invention, Geddes in *The New Scientist,* 12 May 2007 at page 8 (copy submitted), noted that a cancer research scientist at Beth Israel Deaconess Medical Centre (Boston, MA) was "impressed" by the inventors' minicell-based approach. Applicant further argues that "Office personnel should consider all rebuttal arguments and evidence presented by applicants." See, *e.g., Soni,* 54 F.3d at 750, 34 USPQ2d at 1687 (error not to consider evidence presented in the specification)." Applicant provides evidence of use of several small chemotherapeutic drug-packaged minicells that shows significant anti-tumor efficacy (see Brahambhatt's declaration, section A-I, pages 2-11).

Such is found not persuasive because as stated in previous office action unexpected results have to be commensurate with the scope of the invention. "Whether the unexpected

results are the result of unexpectedly improved results or a property not taught by the prior art, the "objective evidence of nonobviousness must be commensurate in scope with the claims which the evidence is offered to support." In other words, the showing of unexpected results must be reviewed to see if the results occur over the entire claimed range. *In re Clemens*, 622 F.2d 1029, 1036, 206 USPQ 289, 296 (CCPA 1980)." In the instant case, claims are not limited to chemotherapeutic agent. It is in this context, it was indicated that claims are broad and read on using any small therapeutic drug. The guidance provided in the specification as well as declaration filed on 12/ 14/2011 is limited to chemotherapeutic drugs. Applicants' declaration is silent in delivering any drug other than chemotherapeutic drug to a target cells.

Should the claims be amended to limit any small molecule drug to chemotherapeutic drug and composition free of bacterial blebs of 200nm or less in size, the above obviousness rejection may be overcome pending further consideration.

Withdrawn-Double Patenting

Claims 8, 16, 19-22 were provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 40-44, 48-51 and 73 of copending Application No. 11/765635. It is noted that Applicants' cancellation of claims 40-44, 48-51 and 73 in application no '635 renders their rejection moot.

Conclusion

No claims allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Denyer, S.P., and Maillard, J.-Y. (2002. J. Appl. Microbiol. (Suppl. 92), 35S–45S), Frazer et al (Journal of Bacteriology, 1973, 615-622). Tomlinson I et al (.Methods Enzymol, 2000, 326, 461-479) teach a method for generating multivalent and bispecific antibody fragments.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ANOOP SINGH whose telephone number is (571)272-3306. The examiner can normally be reached on 9:00AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272- 4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/Anoop Singh/
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